

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION See paragraph 2 below

International application No.
PCT/EP2005/002641

International filing date (day/month/year)
11.03.2005

Priority date (day/month/year)
19.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D277/82

Applicant
DIPHARMA S.P.A.

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of the opinion

- 1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
 claims Nos. 14,15

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos. 14,15
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
the written form has not been furnished
 does not comply with the standard
the computer readable form has not been furnished
 does not comply with the standard
 the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 See separate sheet for further details

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Box No. IV Lack of unity of Invention

- 1. In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
 - paid additional fees.
 - paid additional fees under protest.
 - not paid additional fees.
- 2. This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
- 3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
 - complied with
 - not complied with for the following reasons:

see separate sheet
- 4. Consequently, this report has been established in respect of the following parts of the international application:
 - all parts.
 - the parts relating to claims Nos. 1-13,16,17

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	2,4-13,16,17
	No:	Claims	1,3
Inventive step (IS)	Yes:	Claims	2,4-13,16,17
	No:	Claims	1,3
Industrial applicability (IA)	Yes:	Claims	1-13,16,17
	No:	Claims	

2. Citations and explanations

see separate sheet

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Box No. VI Certain documents cited

- 1. Certain published documents (Rules 43bis.1 and 70.10)
and / or
- 2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV
Lack of unity of invention

The application is directed to preparation processes of pramipexole. Pramipexole as well as processes for its preparation are known. The problem to be solved by the present application is to find further preparation processes for pramipexole.

In order for a group of inventions to be unitary Rules 13.1. and 13.2. PCT require a (corresponding) special technical feature to be present which links the claims together to form a single general inventive concept. For claims 1-13, 16, 17 this feature is the use of a Curtius-like rearrangement of compound (I) to the amines (VII) in the preparation of pramipexole together with the corresponding intermediates. Claims 14 and 15 however are directed to the synthesis of pamiprexole starting from the known (see e. g. J. Med. Chem 30, 494 (1987), cited in the description)) amines (VII) characterized by an acylation/reduction process. These two groups of claims are not linked to form a single general inventive concept by any special technical feature. The application provides thus two different unrelated solutions for the above stated problem; the first group proposes a different intermediate, the second different reaction conditions.

The two groups of inventions are thus:

1. Claims 1-13,16,17

compounds (I), their use in the preparation of pramipexole and intermediates (ia), (ib), (lc) and (le)

2. Claims 14,15

preparation of pramipexole by acylation of compounds (VII) using propionic acid anhydride and subsequent reduction with an alkali metal borohydride and molecular iodine

Since no fees have been paid for the second group of inventions, the following examination covers only the first group.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art

The following documents have been cited:

- O D1: US-A-4 988 699 (CAPRATHE ET AL) 29 January 1991 (1991-01-29)
- D2: SCHNEIDER C S ET AL: "Dopamine autoreceptor agonists: resolution and pharmacological activity of 2,6-diaminotetrahydrobenzothiazole and aminothiazole analogue of apomorphine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 30, no. 3, March 1987 (1987-03), pages 494-498, XP002186199 ISSN: 0022-2623
- D3: WO 2004/083218 A (ACTELION PHARMACEUTICALS LTD; CAROFF, EVA; STEGER, MATTHIAS; VALDENAIR) 30 September 2004 (2004-09-30)

D3 is a P-document and will be disregarded during the PCT procedure.

References to these documents in the following paragraph refer to the passages cited in the search report, if not stated otherwise.

V-2. Novelty (Art. 33(2) PCT)

D1 generically discloses compounds according to claim 1. Present claim 1 does not contain any new structural element that could confer novelty over the disclosure of D1 (note that the different possible protecting groups are specifically mentioned for R in column 2 and also the attachment point in 6-position is exemplified). Claims 1 and 3 are thus not novel.

Claims 4, 5 and 7 are considered novel over the disclosure of D1 since D1 does not

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AUTHORITY (SEPARATE SHEET)**

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mention the resolution of the racemate of carboxylic acids/esters (I). Claims 2 and 6 are novel over D1 since these specific compounds are not disclosed.

D2 discloses only tetrahydrobenzothiophenes with N-bound substituents and is thus not relevant for claim 1.

Claims 8-14 and 16 are novel over D1 because in D1 no pramipexole is prepared and over D2 because of the use of compounds (I) as synthesis intermediates. Claim 17 is novel because these synthesis intermediates are not disclosed in the cited documents.

O **V-3. Inventive step (Art. 33(3) PCT)**

The problem to be solved by the present application was the provision of further preparation processes for pramipexole. Closest state of the art is D2 which discloses a different process. There is no indication in the cited documents that also carboxylic acids (I) could be used as key intermediates in a Curtius-type rearrangement. Novel part of the claims fulfil thus Art. 33(3) PCT.

O **V-4. Industrial applicability (Art. 33(4) PCT)**

Claim 17 is i. a. directed to compounds (Ib). These compounds are carboxynitrenes and thus reactive intermediates in a reaction mechanism. The ISA is of the opinion that such hypothetic molecules lack industrial applicability.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
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AUTHORITY (SEPARATE SHEET)**

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wo2004/083218

30.09.2004

22.03.2004

20.03.2004

Re Item VIII

Certain observations on the international application

Claim 8 is drafted as "use of compounds (I) for the preparation of pramipexole". This drafting is considered unclear (Art. 6 PCT) since it does not specify in which type of reaction they are used and whether they are used as intermediates or in a different way. It also appears that the application does not disclose any other process than the ones claimed in claims 9-13 so that a claim to such an unspecified use lacks support in the description (Art. 6 PCT).